Green chemistry: synthesis in micro reactors

Tutorial Review

Stephen J. Haswell and Paul Watts*

Department of Chemistry, University of Hull, Cottingham Road, Hull, UK HU6 7RX. E-mail: p.watts@hull.ac.uk

Received 25th October 2002
First published as an Advance Article on the web 10th February 2003

The importance of minimizing the impact that chemical processing has on the environment is growing, with an increased appreciation of the need to reduce pollution and the depletion of our finite environmental resources. Optimal use of material, energy and consequent waste management can be recognised as important factors for environmental protection. In the case of minimising waste there are two approaches, the traditional approach aims at reducing waste at the end of the pipeline, for example, decreasing emission by catalytic incineration of exhaust fumes. The second approach is based on minimising waste at the source. In this case, innovative procedures have to be employed to change both the method and the technology used throughout the production cycle. The miniaturisation of chemical reactors offers many fundamental and practical advantages of relevance to the pharmaceutical and fine chemicals industry, who are constantly searching for controllable, information rich, high throughput, environmentally friendly methods of producing products with a high degree of chemical selectivity. Indeed, for pharmaceutical companies an informatics-based approach, that micro reactor chemistry can uniquely deliver, may be the trigger for a step change in processes. This review explores how miniaturisation may revolutionise chemical synthesis, highlighting in particular the environmental benefits of this new technology, which include solvent free mixing, *in situ* reagent generation and integrated separation techniques. Furthermore, the possibility of preparing the chemicals in the required volume at point of use, negates the need to store and transport hazardous materials.

1 Introduction

In their simplest form, micro reactor devices consist of a network of micron-sized channels (typical dimensions are in the range 10–300 μm) etched into a solid substrate (see, for example refs. 1–9 for introductory overviews). For solution-based chemistry, the channel networks are connected to a series of reservoirs containing chemical reagents and products to form the complete device or 'chip' with overall dimensions of a few cm.

Reagents can be brought together in a specific sequence, mixed and allowed to react for a specified time in a controlled region of the channel network using electrokinetic (electro-osmotic and electrophoretic) or hydrodynamic pumping. For electrokinetically-driven systems, electrodes are placed in the appropriate reservoirs to which specific voltage sequences can be delivered under automated computer control. This control offers a simple but effective method of moving and separating reactants and products within a micro reactor, without the need for moving parts. Hydrodynamic pumping uses conventional, or micro-scale pumps (notably syringe pumps) to manoeuvre solutions around the channel network, however this technique has the disadvantage of requiring either large external pumps or complex fabrication of small moving parts.

The largest research effort in the field of micro scale devices to date has been in analytical science, where the aim has been to develop a Miniaturised Total Analytical System (μ-TAS).[10–17] Alongside the continuing development of μ-TAS and related analytical applications, a concerted effort has now begun to establish the benefits that micro reactors can bring to the field of reaction chemistry. For example, the ability to manipulate reagent concentrations in both space and time within the channel network of a micro reactor, provides an additional level of reaction control which is not attainable in bulk stirred reactors where concentrations are generally uniform. Furthermore, the spatial and temporal control of chemical reactions in micro reactors, coupled with the features of very small reaction volumes and high surface interactions, is somewhat akin to the situation of reactions within biological cells. Nature exploits the organised distribution of reagents within the micron-sized sub-domains of cells to control and alter chemical reactivity relative to the situation of homogeneous solutions, in a rapid and efficient manner. Consistent with this notion, many reactions have been demonstrated to show altered reactivity, product yield and selectivity when performed in micro reactors as compared with conventional bench top glassware.

To date, the outcome of the reported research has confirmed that micro reactor methodology is applicable to performing both gas and liquid phase reaction chemistry. From the work cited in this review article, the evidence is that the unique *modus operendi* of micro reactors, namely the low-volume spatial and

Green Context

Traditional chemical manufacturing is heavily based on economy of scale with large reactors and associated plants requiring large process batches and associated large scale transport and storage of raw materials and products. All these large scale features present health and safety problems which can lead to major disasters as well as unacceptable levels of risk to operators and the neighbouring community. Microreactor chemistry shows great promise as a novel method on which to build new chemical technology and processes. The desired product is often produced in higher yield and purity, and more quickly. Reactions are much easier to control thus minimising risk and side reactions. Furthermore, solvent free mixing, *in-situ* reagent generation and integrated separation techniques can all help green the chemistry. ***JHC***

 DOI: 10.1039/b210539j

temporal control of reactants and products in a laminar flow diffusive mixing environment in which distinctive thermal and concentration gradients exist, offers a novel method for the chemical manipulation and generation of products. In short, micro reactors are new, safe and more atom efficient tools with which to generate molecules and increase our knowledge of complex chemical processes.

The technology is still in its early development stage and it would be presumptuous at this point to expand too far on the potential applications that micro reactors will find, but some early trends are clear. In the authors' experience, reactions performed in a micro reactor invariably generate relatively pure products in high yield, in comparison to the equivalent bulk reactions, in much shorter times and in sufficient quantities to perform full instrumental characterisation. One of the immediate and obvious applications is therefore in drug and process discovery, where the generation of compounds either with different reagents or under variable conditions is an essential factor. In addition, the opportunity to establish optimal chemical processes including reaction and formulation is an exciting capability of the technology, which could be integrated to appropriate analytical instrumentation. An interesting twist to the chemistry carried out to date in the authors' laboratories is not just the opportunity to separate reactants and products in real time but also the capability to manufacture and use reagents *in situ*. In this review, a brief description of the fabrication and operation of micro reactors is outlined, followed by a detailed description of the type of reactions that can be performed in micro reactors. The environmental significance of performing the reaction in micro reactors, compared with traditional techniques, is subsequently highlighted.

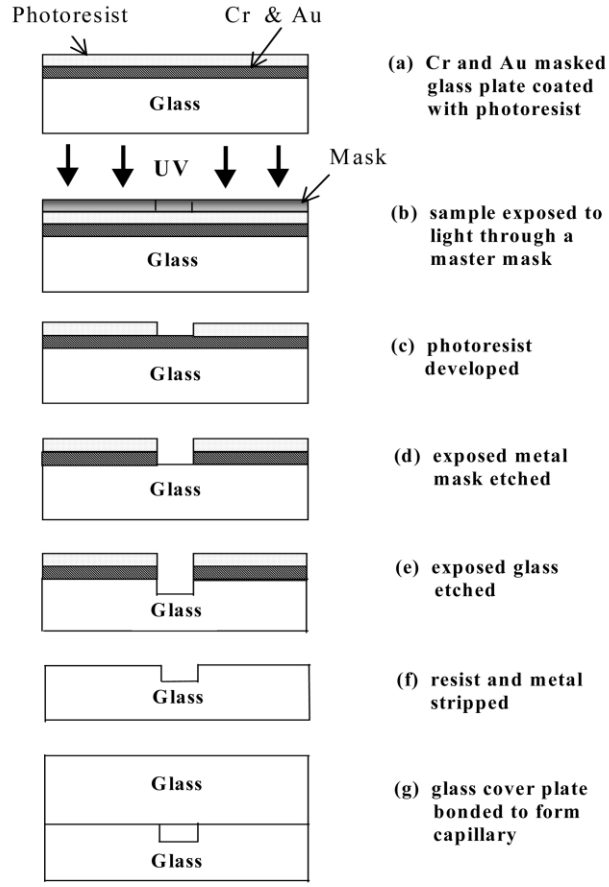


Fig. 1 Photolithographic fabrication of micro reactors.

2 Fabrication of micro reactors

A number of materials such as silicon, quartz, glass, metals and polymers have been used to construct micro reactors.[11] Important considerations in material choice include chemical compatibility, ease and reproducibility of fabrication, whether or not the material supports electroosmotic flow (EOF) with the solvents of interest and compatibility with detection methods. Glass is a popular choice since it allows EOF with many common solvents, is chemically inert, enables the use of visible light detection and fabrication methods are well established.

Depending on the material used, a range of channel microfabrication methods such as photolithography, hot embossing, powder blasting, injection moulding and laser micro forming are available.[18] For glass micro reactors, photolithographic fabrication of channel networks is performed as shown schematically in Fig. 1 and described in refs. 19 and 20. First, the channel network is designed and printed using suitable computer drawing software and a film negative of the desired final size is then prepared by photoreduction to form the optical mask. Commercially supplied borosilicate glass photolithographic plates (thickness 3 mm) coated with a thin metal etch mask layer (normally chromium) plus an upper layer of positive photoresist (0.5–2.0 μm depth) are used for channel network fabrication. The pattern of the required network of interconnecting channels is transferred from the optical mask to the photoresist layer. After light exposure, the photoresist is developed and removed, together with the chromium layer, to reveal the areas of glass to be etched. The channels are then etched using a mixture of 1% HF and 5% NH_4F in water at 65 °C, resulting in an etch rate of 0.3–0.5 μm min^{-1}. During the etching process it is important that the system is well agitated to ensure consistent supply of etchant to the surface plus removal of etch debris.

The base plate containing the etched channel network must next be sealed by bonding to an upper plate (17 mm thick) containing pre-drilled holes which act as reservoirs for reagents and products. In our laboratories, the upper plate is aligned with the channel geometry and thermally bonded to the base plate (typically 575 °C for 3 h).[19,20] Thermal bonding is aided by placing a weighting block of non-adhering quartz of high softening temperature on the upper plate. A photograph of an all-glass device produced by the method described is shown in Fig. 2. For good thermal bonding, it is important to ensure that

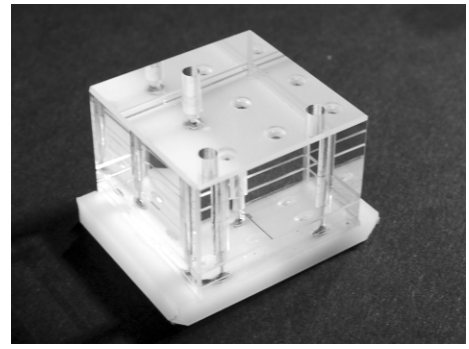


Fig. 2 A borosilicate glass micro reactor.

both the glass types of the upper and lower plates have the correct thermal softening and expansion properties. In addition, the surfaces to be bonded must be clean and flat.

More recently the thermal bonding of ceramic adaptors has enabled hydrodynamic pumping to be more effectively realised.[19] Fig. 3 shows a glass micro reactor with ceramic adaptors enabling HPLC type fittings to be connected directly to the chip.

Fabrication in polymeric materials, whilst attractive from an engineering and cost perspective, does pose a number of reagent compatibility issues. However, recently, the UK Lab on a Chip

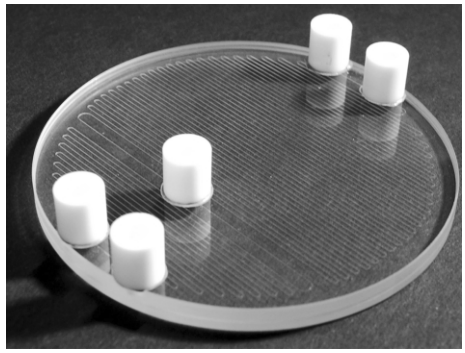


Fig. 3 Micro reactor with ceramic fittings.

Consortium project demonstrated that polymer devices with channels fabricated in SU-8 (an epoxy resin) coated on a polymer support (such as methacrylate) is relatively robust to chemical attack. The first generation of such devices (Fig. 4) are

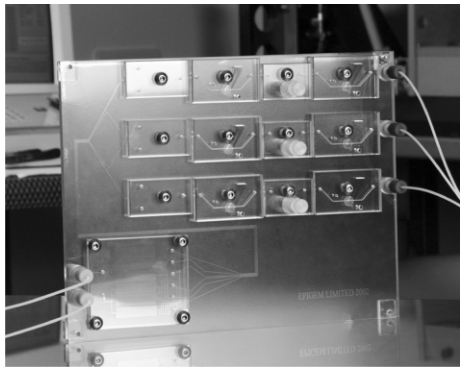


Fig. 4 Micro reactors fabricated from polymers (Photograph courtesy of Epigem Ltd.).

now being evaluated. This methodology has the advantage that the non-wetted bulk of the chip can, if desired, be fabricated from low cost commodity polymers.

Of all the fabrication media, perhaps metals are the most robust in terms of engineering requirements and more specifically, micro mixers have been constructed and applied in chemical processing. This subject is extensively reviewed in ref. 9.

3 Operation of micro reactors using electrokinetic control

Pumping of solutions around a channel network by EOF, using voltages applied *via* electrodes placed in the reservoirs, has several significant advantages over hydrodynamic based pumping methods.[21–24] It can be easily miniaturised since no mechanical moving parts are involved and the required voltage sequences can be readily applied under automated computer control. For a glass micro reactor, the channel wall–solution interface normally has a negative charge, arising from ionisation of surface groups, which are immobile. This immobile surface charge attracts a diffuse layer (of thickness of the order of nm) of mobile, oppositely charged counter-ions in the solution adjacent to the channel wall (cations for a negatively-charged glass channel wall). As shown schematically in Fig. 5, application of an electric field along the channel length causes the nm thick 'skin' of mobile cations to move towards the more negative electrode, which drags all the intervening solution in the bulk of the channel with it. An important feature of EOF is that the liquid EOF velocity is constant across the channel except in the nm thick regions of the diffuse layer of counter-

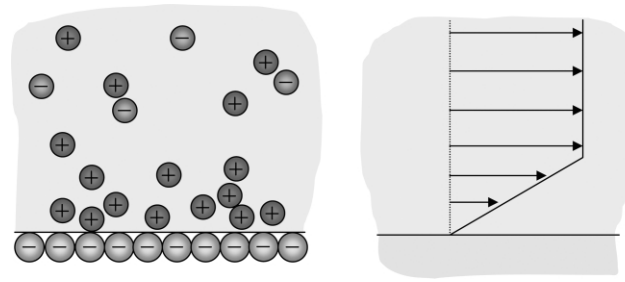


Fig. 5 Profile of electroosmotic flow.

ions very close to the wall. Unlike EOF, pressure-driven flow produces a parabolic velocity profile with high velocities in the channel centre and slow velocities near to the wall, giving rise to increased 'blurring' of reagent zones along a channel length. Imaging of the different velocity profiles induced by EOF and pressure-driven flow has been described by Paul *et al.*[25] It should however be emphasised, that under EOF control, charged solutes move with an electrophoretic velocity in addition to the EOF of the solvent.

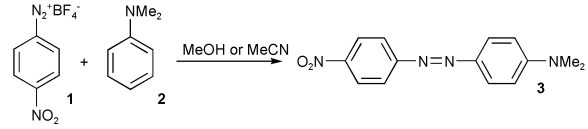
It should be stressed, that for EOF to be achieved polar solvent types need to be used (*e.g.* methanol, DMF, DMSO *etc.*). Clearly this limitation could reduce the scope of micro reactor applications, however the authors are currently developing a combined electrokinetic/hydrodynamic pumping method for manipulating reactants, intermediates and products within a micro reactor device. Such a system offers wider solvent and reagent capability, whilst still enabling the electrophoretic mobility of chemical species to be exploited.

4 Reactions performed in micro reactors

The following section reviews the chemical reactions that have been performed within micro reactor systems to date. The review is divided into three sections, concentrating on solution phase synthesis, catalysed reactions and finally gas phase synthesis.

4(a) Liquid phase reactions

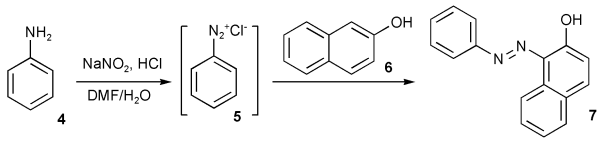
The diazotization of aromatic amines is an industrial process of great importance, however the dangers of diazotization are well known. The explosive nature of diazonium salts necessitates extreme care hence the low volume associated with micro reactors affords a safe route to perform such reactions. Salimi-Moosavi *et al.*[26] have demonstrated the synthesis of diazo dyes within a micro reactor. The authors have reacted 4-nitrobenzenediazonium tetrafluoroborate **1** with *N*,*N*-dimethylaniline **2** in a micro reactor fabricated from glass, to give the red diazo compound **3** (Scheme 1). The reagents were mobilised in



Scheme 1

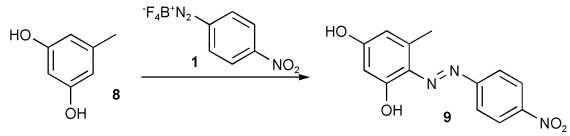
the reactor, using EOF in either a protic (methanol) or an aprotic (acetonitrile) solvent, to give conversions of 37 and 22%, respectively.

In comparison Wootton *et al.*[27] have demonstrated the synthesis of azo dyes using hydrodynamic pumping within a micro reactor. The authors demonstrated that aniline **4** could be converted into the diazonium salt **5** before being reacted *in situ* with β-naphthol **6** to form the azo dye **7** in up to 52% overall conversion (Scheme 2).



Scheme 2

Hisamoto *et al.*[28] have described the first example of a phase-transfer reaction in a micro reactor. The authors have successfully conducted a phase-transfer diazo coupling reaction in which a solution of 5-methylresorcinol **8** in ethyl acetate was reacted with an aqueous solution of 4-nitrobenzenediazonium tetrafluoroborate **1** to form the azo dye **9** (Scheme 3). Syringe

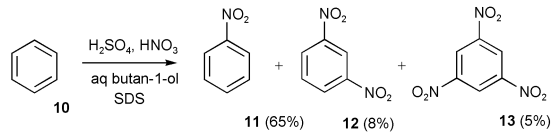


Scheme 3

pumps were used to move the reagents around the reactor manifold and the authors report that the product was isolated in 100% yield.

Nitration reactions also represent an important but hazardous process, in which the use of excess quantities of concentrated nitric and sulfuric acids are used. The reactions are extremely exothermic and it is hence difficult to control the temperature of such reactions when performed on a large scale. As a result, micro reactors have a considerable attraction for these reactions because the reactor enables not only excellent temperature control of the reaction but also product selectivity.

Doku *et al.*[29] have reported the nitration of benzene **10** in a borosilicate glass micro reactor. The benzene was mobilised by electroosmotic flow as a microemulsion using the surfactant, sodium dodecyl sulfate (SDS). The nitronium ions, which were produced *in situ* by mixing sulfuric and nitric acids, underwent electrophoretic-induced mobility (*i.e.* the ions not the reagents moved). A co-solvent, butan-1-ol, was used to enhance the solubility of the benzene in the aqueous system. The authors report that mononitration occurs in 65% conversion to give nitrobenzene **11** (Scheme 4) and that approximately 8% of

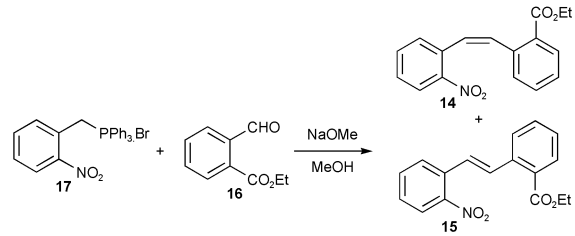


Scheme 4

1,3-dinitrobenzene **12** and 5% of 1,3,5-trinitrobenzene **13** were obtained. Importantly, Doku *et al.* demonstrated that it is possible to mobilise a non-polar liquid, such as benzene, using EOF by dissolving it in a two-phase microemulsion system.

Burns and Ramshaw[30] have also investigated the nitration of benzene and toluene in a micro reactor. They have reported that the conversion has a linear relationship with temperature. More interestingly, they have demonstrated that the conversion may be increased, by reducing the dimensions of the micro reactor channels. They found that reducing the capillary diameter from 250 to 130 nm more than doubled the rate of nitration. The flow rates were additionally determined to be critical, with faster flow rates giving higher conversions. The authors postulate that the increased flows promoted increased mixing within the channels.

Skelton *et al.* have reported the application of micro reactors, prepared from borosilicate glass, for the Wittig reaction.[31,32] The authors used the micro reactor to prepare the *cis*- and *trans*-nitrostilbene esters **14** and **15** using the Wittig reaction (Scheme 5). A number of features such as stoichiometry and stereochemistry were investigated. When two equivalents of the aldehyde **16** to the phosphonium salt **17** were used in the reaction, a conversion of 70% was achieved. The micro reactor

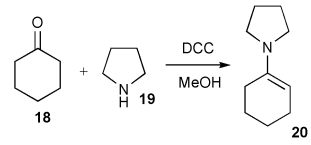


Scheme 5

demonstrated an increase in reaction efficiency of 10% over the traditional batch synthesis. The reaction stoichiometry was subsequently reduced to 1:1, but using a continuous flow of reagents, as above, the conversion was poor (39%). The conversion was increased to 59% using an 'injection' technique, where 'slugs' of the phosphonium salt **17** were injected into a continuous flow of the aldehyde **16**.

The research was further extended to investigate the stereochemistry of the reaction. The ratio of isomers **14** and **15** was controlled by altering the voltages applied to the reagent reservoirs within the device, which in turn affected the EOF and electrophoretic mobility of the reagents. The variation in the external voltage subsequently altered the relative reagent concentration within the device, producing *cis*/*trans* ratios in the region 0.57–5.21. In comparison, the authors report that, when a traditional batch synthesis was performed based on the same reaction time, concentration, solvent and stoichiometry, a *cis*/*trans* ratio of approximately 3:1 was observed. This demonstrated that significant control was possible in a micro reactor compared with batch reactions.

Sands *et al.*[33] have recently reported the preparation of enamines in a micro reactor. Enamines are traditionally prepared under Dean and Stark conditions, where the ketone and secondary amine are heated to reflux in toluene. These conditions remove the water from the reaction to produce the equilibrium-dependent enamine. Using the micro reactor, cyclohexanone **18** was reacted with pyrrolidine **19** using methanol as the solvent, in the presence of dicyclohexylcarbodiimide (DCC), to form the enamine **20** in 42% conversion at room temperature (Scheme 6). Clearly the use of



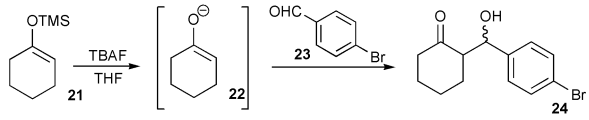
Scheme 6

methanol as solvent at room temperature, compared with the traditional conditions, represents a more environmentally friendly procedure. In this case also, the electrophoretic mobility of the product is thought to be greater than that of water, so enabling product separation and purification *in situ*.

Carbanion chemistry is one of the most common methods of C–C bond formation used in the pharmaceutical industry. In such reactions large volumes of highly pyrophoric bases are frequently employed. In addition, large quanties of heat are frequently generated which means that careful control of the temperature, to prevent by-product formation, is required. Hence, micro reactors have a considerable attraction for these reactions because the reactor enables excellent temperature control of the reaction.

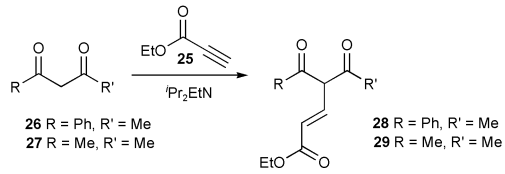
Wiles *et al.*[34] have recently demonstrated the use of silyl enol ethers in the aldol reaction within a micro reactor. Quantitative conversion of the silyl enol ethers to β-hydroxyketones was observed in 20 min compared to traditional batch systems, where quantitative yields were only obtained when extended reaction times of up to 24 h were employed. One example involved the treatment of the TMS enol ether **21** with tetra-*n*-butylammonium fluoride (TBAF), to generate the tetra-*n*-

butylammonium enolate **22** *in situ*, followed by condensation with *p*-bromobenzaldehyde **23** to give the β-hydroxyketone **24** in 100% conversion (Scheme 7).



Scheme 7

Wiles *et al.*[35] have also reported the preparation of the enolates from a series of 1,3-diketones using an organic base and their subsequent reaction with a variety of Michael acceptors such as **25** to afford 1,4-addition products within a micro reactor (Scheme 8).

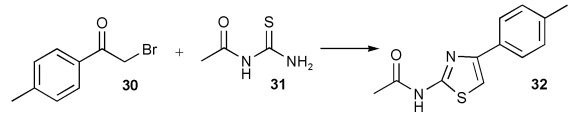


Scheme 8

When using a continuous flow of the reagents **25** and **26**, 15% conversion to the adduct **28** was observed, compared with 56% when the diketone **27** was reacted with **25** forming the Michael adduct **29**. The authors, however, demonstrated enhancements in conversions through the application of the stopped flow technique. This procedure involved the mobilisation of reagents through the device for a designated period of time, using an applied field, and the flow was subsequently paused by the removal of the applied field, prior to re-applying the field. Using the regime of 2.5 s on and 5 s off, the conversion to the product **28** was improved to 34%, while lengthening the stopped flow period to 10 s, resulted in a further increase to 100%. This was compared to the preparation of **29**, in which the regime of 2.5 s on and 5 s off resulted in an increase in conversion to 95%. This demonstrated that the enolate of 2,4-pentanedione **27** was more reactive than the corresponding enolate of benzoyl acetone **26**. The authors propose that the observed increase in conversion, when using the technique of stopped flow, was due to an effective increase in residence time within the device corresponding to the different kinetics associated with these reactions. This approach is clearly relevant to those wishing to study reaction kinetics of such reactions.

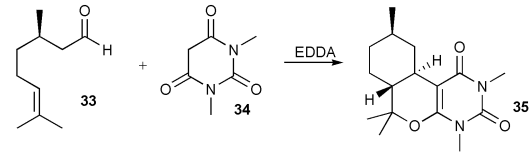
Although the previous result demonstrates the ease with which reaction conditions may be optimised, it is still sometimes necessary to heat reactions in order to achieve high yields of products. Industrially, special equipment is required when performing large-scale reactions at elevated temperature. However, Garcia-Egido *et al.*[36] at GlaxoSmithKline have demonstrated the synthesis of 2-aminothiazoles using a Hantzsch synthesis within a micro reactor. The paper represents the first example of a heated reaction using an organic solvent, within a glass micro reactor under EOF conditions. During the experiments the T-shaped micro reactor was heated to 70 °C using a Peltier heater, which was aligned with the channels and the heat generated by the device was applied to the base of the micro reactor. Reaction of α-bromoketone **30** with thiourea **31**, using *N*-methylpyrrolidine (NMP) as solvent, resulted in the preparation of aminothiazole **32** in up to 85% conversion (Scheme 9).

Fernandez-Suarez *et al.*[37] have reported the synthesis of cycloadducts in a micro reactor using hydrodynamic driven flow. The reactions consisted of Knoevenagel condensation of an aldehyde **33** with a 1,3-diketone **34** in the presence of



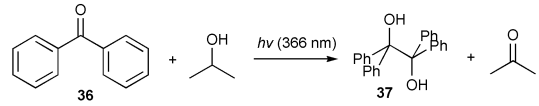
Scheme 9

ethylenediamine acetate (EDDA) as catalyst, in aqueous methanol as solvent. The reaction intermediate underwent an intramolecular hetero-Diels–Alder reaction to form cycloadduct **35** in 60–68% conversion (Scheme 10).



Scheme 10

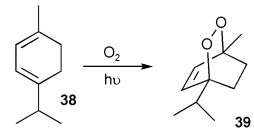
Environmentally attractive photochemically induced reactions are problematic on a large scale because many chemical species strongly absorb the light, effectively reducing the path length, even when powerful irradiation is used. Hence better results are obtained when the desired reaction is scaled down in size and Jenson and coworkers[38] have reported a photochemical reaction within a micro reactor. The reactor was fabricated by bonding a patterned silicon wafer to a quartz wafer, the advantage of this fabrication technique being that the quartz substrate allows reaction and detection using UV light of lower wavelengths than permitted by Pyrex substrates. The authors investigated the pinacol formation reaction of benzophenone **36** using propan-2-ol as solvent (Scheme 11). The reaction is



Scheme 11

known to follow a radical reaction pathway[39] and it is reported that the longer the residence time of the reaction, the greater the conversion to benzopinacol **37**. The authors report that there was no detectable product formation for flow rates greater than 10 μl min^{-1}. With reduced flow rates, having larger residence times, the conversion improves because the amount of light absorbed increases and there is therefore sufficient time for the excited species to diffuse and react with the benzophenone. The authors report conversions of up to 60% when using flow rates of 4 μl min^{-1}.

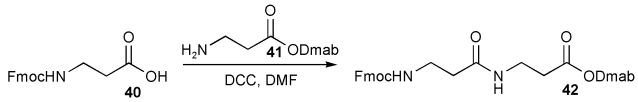
Using a similar approach Wootton *et al.*[40] investigated the photochemical generation of singlet oxygen within micro reactors. The technique allows the generation of singlet oxygen without the inherent dangers of forming large quantities of potentially explosive oxygenated solvents. The singlet oxygen was formed within the reactor channel by irradiation with a 20 W, 6 V tungsten lamp. The authors have used the aforementioned conditions to convert α-terpinene **38** into ascaridole **39** (Scheme 12) in greater than 80% conversion. For safety,



Scheme 12

nitrogen degassing of the product mixture was undertaken as soon as the solution was collected, hence avoiding accumulation of oxygenated solvents.

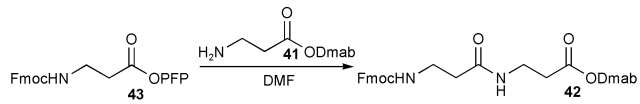
Watts *et al.* have recently demonstrated the first example of a multi-step synthesis in a micro reactor where they have used their devices in peptide synthesis.[41,42] The authors evaluated the reactor using a carbodiimide coupling reaction of Fmoc-β-alanine **40** (Fmoc = fluorenylmethoxycarbonyl) with the amine **41** to give the dipeptide **42** (Scheme 13). When stoichiometric



Scheme 13

quantities of the reagents were used, only *ca.* 10% conversion to the dipeptide **42** was achieved. By using two equivalents of dicyclohexylcarbodiimide (DCC), however, an increase in conversion to *ca.* 20% was observed and by applying a stopped flow technique (2.5 s injection length with stopped flow for 10 s), the conversion of the reaction was further increased to approximately 50%. Using five equivalents of DCC, a conversion of up to 93% of the dipeptide **42** was obtained using the stopped flow technique.

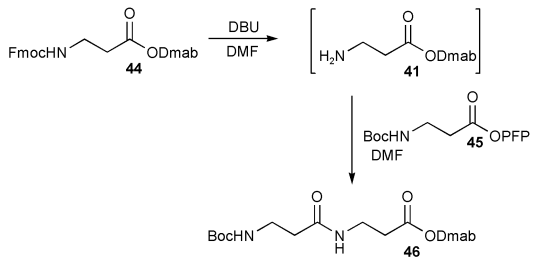
The authors also demonstrated that the dipeptide could be prepared from pre-activated carboxylic acids.[41,42] They report that the reaction of the pentafluorophenyl (PFP) ester of Fmoc-β-alanine **43** with the amine **41** gave the dipeptide **42** quantitatively in 20 min (Scheme 14). This represented a



Scheme 14

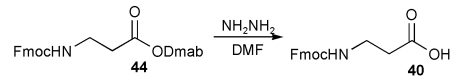
significant increase in yield compared with the traditional batch synthesis, where only a 50% yield was obtained in 24 h.

Having demonstrated that peptide bonds could be successfully formed when using a micro reactor, the authors then found that they could extend the methodology to the preparation of longer-chain peptides. Using the micro reactor, the Dmab ester (Dmab = 4-[*N*-(1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl)-3-amino]benzyl) of Fmoc-β-alanine **44** was reacted with one equivalent of piperidine or 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU)[43,44] to give the free amine **41** in quantitative conversion. This is in comparison to solid phase peptide synthesis where 20% piperidine in DMF is frequently employed, which demonstrates the atom efficiency of reactions performed within the devices. The authors then reacted the amine *in situ* with the pentafluorophenyl ester **45** to give the dipeptide **46** (Scheme 15) in 96% overall conversion.



Scheme 15

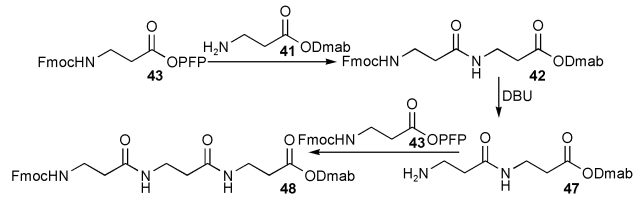
Having shown that more complex peptides could be produced by removal of the *N*-protecting group, the authors then demonstrated that they could remove the Dmab ester using hydrazine. The reaction of the Dmab ester **44** with one equivalent of hydrazine resulted in quantitative deprotection, to afford the carboxylic acid **40** (Scheme 16). This is in



Scheme 16

comparison to the solid phase peptide synthesis where 2% hydrazine in DMF is generally required to effect complete deprotection.[45]

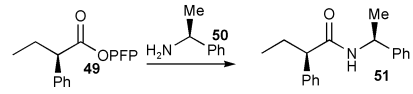
The authors have further extended the approach to the synthesis of tripeptide **48**.[42] Reaction of pentafluorophenyl ester **43** with amine **41** formed dipeptide **42**, which was reacted with DBU to effect Fmoc deprotection. The amine **47** was then reacted *in situ* with another equivalent of pentafluorophenyl ester **43** to prepare tripeptide **48** in 30% overall conversion (Scheme 17). The approach clearly demonstrates that inter-



Scheme 17

mediates may be generated *in situ* and used in subsequent reactions. Although in the above examples the intermediates are relatively non-toxic, it is postulated that the approach may be used to generate highly toxic reagents *in situ*, that one would rather not use in a large-scale synthesis.

Having demonstrated that peptide bonds could be successfully formed when using a micro reactor, the authors then investigated racemisation in peptides derived from α-amino acids.[46] Reaction of the pentafluorophenyl ester of (*R*)-2-phenylbutyric acid **49**, at 0.1 M concentration, with α-methylbenzylamine **50**, gave the product **51** in quantitative conversion with 4.2% racemisation (Scheme 18). Importantly

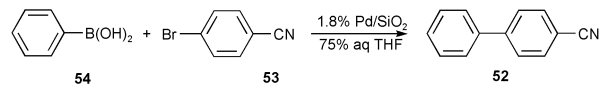


Scheme 18

there was less racemisation than observed in the batch reaction at the same concentration and temperature. The reduced level of racemisation was attributed to the reduced reaction times observed within the micro reactors.

4(b) Catalytic reactions

Greenway *et al.* have demonstrated the Suzuki reaction within a micro reactor.[47] This represented an example of heterogeneous catalysis where 1.8% palladium on silica was placed in the central channel of the micro reactor. The catalyst was immobilised between microporous silica frits prepared from potassium silicate and formamide. The micro reaction was optimised using flow injection analysis principles, producing a conversion of 67% of cyanobiphenyl **52** at room temperature. The flow injection method adopted allowed the periodic injection of the aryl halide **53** into a continuous flow of the phenylboronic acid **54** (Scheme 19). Traditionally, tetra-



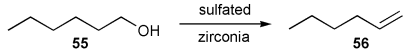
Scheme 19

hydrofuran (THF) is used as the solvent in this reaction, however as has been found with many organic solvents THF has

very low natural EOF properties and for this reason, it was mixed with water (75 : 25) for use in the reaction. The yields obtained were comparable with Suzuki reactions on a batch scale using homogeneous catalysis. Importantly, there were negligible levels of the palladium catalyst in the product, which was demonstrated using inductively coupled-mass spectrometry (ICP-MS), this illustrating that the catalyst was not leaching from the reactor.

One of the interesting observations of the reaction was that, unlike conventional Suzuki reactions, an additional base was not required. Although the exact reason for this is not clear, it is postulated that the electric field may be sufficient to cause ionisation of the water at the catalyst surface. It is feasible that the hydroxide formed in this way may be sufficient to perform the function of the conventional organic or inorganic base. Alternatively, it has been subsequently proposed that a more basic environment may be formed at the surface of the micro reactor. Once again this effect could have wider implications in the field of clean chemistry.

Wilson and McCreedy[48] have reported the use of a micro reactor to perform the dehydration of hexan-1-ol to hex-1-ene, using a sulfated zirconia catalyst. The micro reactor was fabricated from a glass plate, which was etched using photolithography. A PDMS top block, with pre-drilled holes to act as reservoirs for the reagents, was then aligned with the channel geometry. In order to introduce the catalyst into the micro reactor, it was dusted over the surface of the PDMS face before the base plate was joined to the top plate. This process immobilised the catalyst, while simultaneously increasing its surface area. The overall effect was to produce a catalytically-active wall of the microchannel. A heater, fabricated from Nichrome wire, was also immobilised in the top plate. Pumping was produced with a syringe pump and the products were analysed by gas chromatography (GC). The conversion of hexan-1-ol **55** to hex-1-ene **56** was between 85 and 95% with no additional products being detected (Scheme 20). This yield is

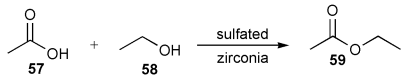


Scheme 20

extremely good when compared to the 30% yield expected for the industrially used process.

The reaction was also applied to ethanol. At a reaction temperature of 155 °C and using a syringe pump at a flow rate of 3 μl min^{-1}, the product collected was found to contain 68% ethene, 16% ethane and 15% methane, together with trace amounts of ethanol. When electroosmotic pumping was used, the flow rate was between 0.9 and 1.1 μl min^{-1} at a field strength of 200 V cm^{-1}. The only detectable product was methane, indicating that the reaction had progressed beyond dehydration to complete cracking of the ethanol. Additionally, trace amounts of methanol were present in the product. It is proposed that the slow flow rate of the electroosmotic pumping, resulted in longer residence times in the reactor. EOF however cannot be applied to all reactions because organic reactants, such as hexanol, exhibit no natural EOF under an applied potential.

The authors used the same device to investigate esterification reactions, where a 1 : 1 mixture of acetic acid **57** and ethanol **58** was pumped through the micro reactor using a syringe pump at a flow rate of 2 μl min^{-1} to produce ethyl acetate **59** (Scheme 21).[49] By increasing the temperature of the reaction from room temperature to 180 °C, the conversion of the reaction was

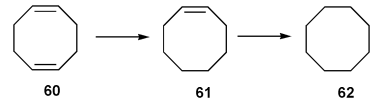


Scheme 21

increased to about 30%. Although the preliminary yield was not great, the procedure has environmental advantages compared to the traditional conditions used in esterification reactions.

4(c) Gas phase reactions

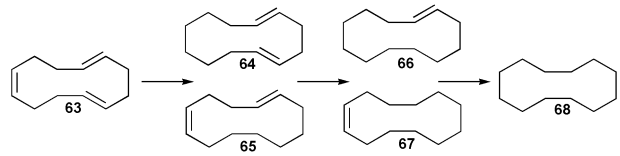
Hönicke and coworkers[50] have reported the gas phase partial oxidation of cyclic dienes, to their corresponding monoalkenes, over palladium and ruthenium/zinc catalysts. The micro reactors consisted of aluminium wafers, with mechanically-etched channels, which were activated by anodic oxidation to obtain a porous oxide layer, which was used as the catalyst support. Impregnation of an organic solution of palladium(II) acetylacetonate resulted in microchannels consisting of an 18 μm thick layer of 0.18% Pd catalyst. The wafers were then stacked in a stainless steel housing to form a micro reactor consisting of 672 microchannels for a stream of reagents to pass through. The authors used the device to investigate the hydrogenation of 1,5-cyclooctadiene **60** to cyclooctene **61** (Scheme 22). The diene **60** was vapourised and mixed with



Scheme 22

hydrogen, before being passed through the micro reactor at a temperature of 150 °C. By increasing the residence time of the reaction from 35 to 115 ms the authors report that the conversion increased from 75 to 99.5%. Although the increased residence time resulted in increased quantities of cyclooctane **62** being formed, the selectivity of cyclooctene **61** decreased from 99.5 to 98% under these conditions. The procedure represented a novel method for the immobilisation of potentially toxic catalysts, hence the process has possible environmental advantages.

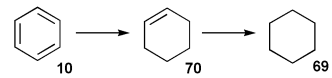
The authors used the same device to investigate the hydrogenation of *cis*,*trans*,*trans*-1,5,9-cyclododecatriene **63** to the cyclododecenes **64** and **65** (Scheme 23). At a temperature of



Scheme 23

150 °C, a selectivity of 85 to 90% was reported, where the conversion was approximately 90%. The selectivity of this reaction was lower than the previous example because of the formation of the by-products **66**, **67** and **68**. It was demonstrated, however, that there was a selectivity advantage of the micro reactor compared to a fixed-bed reactor.

The catalytic hydrogenation of benzene **10** was also investigated (Scheme 24), but complete reduction to cyclohexane **69**



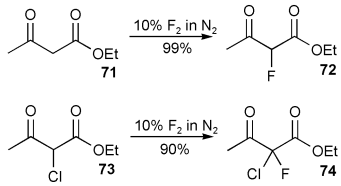
Scheme 24

was observed to take place when using the Pd catalyst. The authors report that hydrogenation of benzene to cyclohexene **70** was accomplished using a micro reactor system consisting of a ruthenium/zinc catalyst, which was incorporated into the micro reactor using the same methodology, but the conversions were

reported to be low (*ca* 10%), with a maximum selectivity of 36%.

The use of elemental fluorine in organic synthesis is problematic as a result of the difficulties associated with the safe handling of gaseous fluorine.[51,52] In addition, fluorination reactions are generally extremely exothermic and it is difficult to control the temperature of such reactions when performed on a large scale. Micro reactors have considerable attraction for direct fluorination processes because there is only a small amount of fluorine in the reactor at any given time. The micro reactor enables excellent temperature control of the reaction as well as an opportunity for scale up, by the simultaneous use of many such reactors.

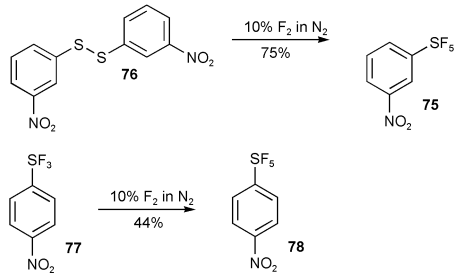
Chambers and Spink[53,54] have reported the use of micro reactors for the fluorination and perfluorination of organic compounds using elemental fluorine. A nickel or copper micro reactor was used for the investigation and the liquid reactants and solvents were introduced into the reaction chamber *via* a syringe using a syringe-pump. Fluorine, in a nitrogen carrier gas, was introduced from a cylinder using a mass-flow controller. The liquid-gas mixing proceeded *via* 'cylindrical flow', where the liquid forms an outer cylinder coating the reactor surface with the gas flowing through the centre. This flow regime has enormous benefits in that it provides very large surface-to-volume ratios for the liquid phase, producing a very efficient reaction over a short distance. The products were trapped in a tube, which was cooled with either a salt/ice bath (0 °C) or an acetone/carbon dioxide bath (−78 °C). The fluorination of β-dicarbonyl compounds proceeded with a high efficiency using 10% fluorine in nitrogen at 5 °C and with formic acid as the solvent. Ethyl acetoacetate **71** was fluorinated in 99% conversion to give ethyl 2-fluoroacetoacetate **72** while ethyl 2-chloroacetoacetate **73** was fluorinated in 90% conversion, yielding ethyl 2-chloro-2-fluoroacetoacetate **74** (Scheme 25). Importantly, under these conditions, no perfluorination of



Scheme 25

the substrates was observed, with only the monofluorinated derivatives being isolated. The authors report that the bulk fluorination of ethyl 2-chloroacetoacetate **73** gives only a low conversion to **74**,[55] illustrating that the flow system is more efficient. This illustrates the catalytic effect of the fluorinated metal surface.

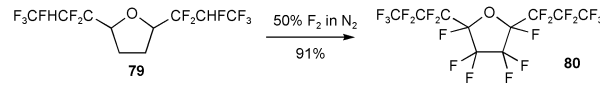
Sulfur pentafluoride derivative **75** was prepared in 75% yield by the reaction of the disulfide **76** with 10% fluorine in nitrogen, using acetonitrile as the solvent (Scheme 26). Similarly,



Scheme 26

treatment of the trifluoride **77** with fluorine gave sulfur pentafluoride derivative **78** in 44% yield.

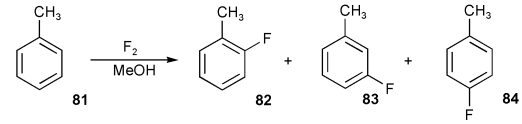
Perfluorination reactions were found to require an additional heating stage for the reaction to go to completion. The reaction of the tetrahydrofuran derivative **79** with 50% fluorine in nitrogen at 280 °C gave the perfluorinated compound **80** in 91% yield (Scheme 27). In conventional reactions, cobalt trifluoride



Scheme 27

would be used to perfluorinate hydrocarbons.[56] Some of the reactions carried out by the authors, however, required much lower temperatures than would be expected if this compound was used.

Jenson and coworkers have also demonstrated the direct fluorination of aromatic compounds in a micro reactor, a process difficult to perform on a conventional scale.[57] The reactor was fabricated from silicon and capped with Pyrex using anodic bonding. The surfaces of the reactor, which were in contact with the reagents, were coated with a nickel film using a metal deposition technique. The authors have used the micro reactor in the fluorination of toluene **81** at room temperature (Scheme 28). Using ten equivalents of fluorine, in methanol as



Scheme 28

the solvent, the authors report an 80% conversion to give the monofluorinated toluenes. The substitution pattern of the *ortho*- **82**, *meta*- **83** and *para*- **84** isomers was determined to be 4 : 1 : 2 by GC.

Srinivasan *et al.*[58] performed the partial oxidation of ammonia using a silicon-based micro reactor. Integrated heaters as well as flow and temperature sensors were fabricated into the sub-mm flow channels. The platinum catalyst was deposited in the reaction channel by electron-beam evaporation *via* a shadow mask. The gaseous reactants were fed from cylinders into the micro reactor by external mass-flow controllers, which maintained the desired flow rates. The product composition was continuously monitored using a mass spectrometer. The authors reported a change in the micro reactor exhaust composition over a range of temperatures and flow rates and they also demonstrated that the conversion and selectivity behaviour of conventional reactors could be reproduced in a micro reactor.

The effective heat transfer of micro reactors provides very accurate temperature control for both exothermic and endothermic reactions, thus eliminating undesired side reactions. An example has been reported by Hessel *et al.*,[59] who demonstrated that a micro reactor could be used to prepare hydrogen cyanide *via* the Andrussow route. In traditional laboratory reactions, the hydrogen cyanide is reported to hydrolyse to ammonia. The use of a microheat exchanger in this experiment, however, prevented this further reaction.

5 Concluding remarks

Micro reactor chemistry is currently showing great promise as a novel method on which to build new chemical technology and processes in which the reactions generally produce the desired product in higher yield and purity, in shorter periods of time, compared with traditional batch reactions. The technology is still in its early development and it would be presumptuous to expand too far on the potential applications that micro reactors will find, but some early trends are clear. One of the immediate and obvious applications is in combinatorial chemistry and drug

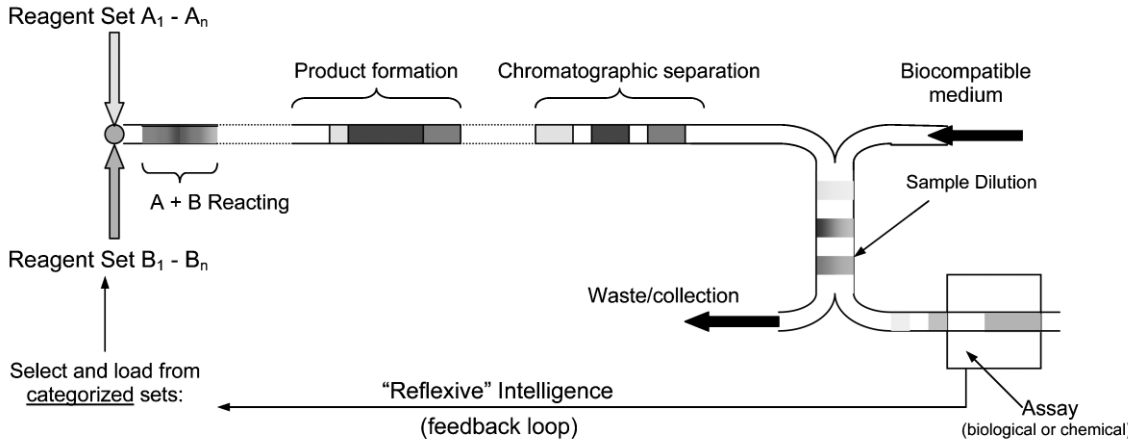


Fig. 6 Integration of a micro reactor with a biological assay system.

discovery, where the generation of compounds with different reagents or under variable conditions is an essential factor. Perhaps more intriguing, is what new angles micro reactors bring to reaction chemistry and these are only now just emerging. For example, extending the heterogeneous catalyst work already described one can see how immobilised or supported reagents could be placed within a device to impart functionality to a reaction whilst maintaining spatial and temporal control. In addition, a microchannel system also provides a potential separation column and integration of a micro reactor device to one of the many highly sensitive microchannel-based biological assay systems may therefore not only be possible, but may also address some of the pharmaceutical industries' potential requirements. Apart from the greatly reduced reaction times demonstrated for the micro reactors, handling times to assay and chemical reagent costs may be virtually eliminated. This paradigm is shown diagramatically in Fig. 6.

Reactions within the micro reactors are found to be more atom efficient, which is of significant environmental importance as this reduces the quantities of raw materials required and minimises waste. Furthermore, the technology allows the temperature of reactions to be controlled, enabling reactions to be conducted safely, where explosion may be observed if the reaction was conducted on a batch scale.

The use of solvent for purification of products is often the largest contributor to waste in a chemical process. Research is currently underway to investigate the purification of chemicals within the micro reactors by exploiting the electrophoretic mobility of the chemical species, which would not require any solvent to be moved within the reactor. This process may be further enhanced through the use of supercritical fluid and ionic liquids, which would be compatible with current micro reactor devices.

In terms of Green Chemistry, micro reactors clearly offer considerable potential in performing safer and more efficient chemical reactions by the use of novel methodologies such as solvent free mixing, *in situ* reagent generation and integrated separation techniques. The capability of producing a parallel network of micro reactors, the so called 'scaling out' of the process, offers a clear route to generating product volume on demand, at the point of use, so reducing the need to store and transport hazardous or reactive chemicals. This is where micro reactors make the greatest contribution to the publics' perception of environmentally clean chemistry.

References

1 D. Bradley, *Eur. Chem.*, 1999, **1**, 17.
2 P. D. I. Fletcher and S. J. Haswell, *Chem. Br.*, 1999, **35**, 38.
3 S. Cowen, *Chem. Ind. (London)*, 1999, 2nd Aug., 584.
4 T. McCreedy, *Chem. Ind. (London)*, 1999, 2nd Aug., 588.
5 D. Barrow, J. Cefai and S. Taylor, *Chem. Ind. (London)*, 1999, 2nd Aug., 591.
6 J. Cooper, D. Disley and T. Cass, *Chem. Ind. (London)*, 2001, 15th Oct., 653.
7 P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong and X. Zhang, *Tetrahedron*, 2002, **58**, 4735.
8 *IMRET 5: Proceedings of the Fifth International Conference on Microreaction Technology*, ed. M. Matlosz, W. Ehrfeld and J. P. Baselt, Springer, Berlin, 2002.
9 W. Ehrfeld, V. Hessel and H. Löwe, *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH, Weinheim, 2000.
10 S. J. Haswell, *Analyst*, 1997, **112**, 1R.
11 A. Manz, D. J. Harrison, E. Verpoorte, J. C. Fettinger, H. Ludi and H. M. Widmer, *Chimia*, 1991, **45**, 103.
12 A. Manz, D. J. Harrison, E. Verpoorte and H. M. Widmer, *Adv. Chromatogr.*, 1993, **33**, 1.
13 A. Manz, C. S. Effenhauser, N. Burggraf, E. Verpoorte, D. E. Raymond and H. M. Widmer, *Anal. Mag.*, 1994, **22**, 25M.
14 *Proceedings of the Micro Total Analytical Systems '98 Workshop*, ed. D. J. Harrison and A. van den Berg, Kluwer Academic Press, Dordrecht, 1998.
15 A. van den Berg and T. S. J. Lammerink, *Top. Curr. Chem.*, 1998, **194**, 21.
16 D. J. Harrison, K. Fluri, K. Seiler, Z. H. Fan, C. S. Effenhauser and A. Manz, *Science*, 1993, **261**, 895.
17 S. C. Jacobson, R. Hergenroder, L. B. Koutny and J. M. Ramsey, *Anal. Chem.*, 1994, **66**, 1114.
18 M. Madou, *Fundamentals of Microfabrication*, CRC Press, Boca Raton, FL, 1997.
19 T. McCreedy, *TrAC, Trends Anal. Chem.*, 2000, **19**, 396.
20 T. McCreedy, *Anal. Chim. Acta.*, 2001, **427**, 39.
21 J. Th. G. Overbeek in *Colloid Science*, ed. H. R. Kruyt, Elsevier, Amsterdam, 1952, vol. 1, ch. V, p. 195.
22 C. L. Rice and R. Whitehead, *J. Phys. Chem.*, 1965, **69**, 4017.
23 R. J. Hunter, *Zeta Potential in Colloid Science*, Academic Press, London, 1981.
24 J. Jednacak, V. Pravdic and W. Haller, *J. Colloid Interface Sci.*, 1974, **49**, 16.
25 P. H. Paul, M. G. Garguilo and D. J. Rakestraw, *Anal. Chem.*, 1998, **70**, 2459.
26 H. Salimi-Moosavi, T. Tang and D. J. Harrison, *J. Am. Chem. Soc.*, 1997, **119**, 8716.
27 R. C. R. Wootton, R. Fortt and A. J. de Mello, *Lab Chip*, 2001, **2**, 5.
28 H. Hisamoto, T. Saito, M. Tokeshi, A. Hibara and T. Kitamori, *Chem. Commun.*, 2001, 2662.
29 G. N. Doku, S. J. Haswell, T. McCreedy and G. M. Greenway, *Analyst*, 2001, **126**, 14.
30 J. R. Burns and C. G. Ramshaw, *IMRET 4: 4th International Conference of Micro Reaction Technology Topical Conference Proceedings, AIChE Spring National Meeting*, March 5–9, 2000, Atlanta, GA, USA, p. 133.
31 V. Skelton, G. M. Greenway, S. J. Haswell, P. Styring, D. O. Morgan, B. Warrington and S. Y. F. Wong, *Analyst*, 2001, **126**, 7.
32 V. Skelton, G. M. Greenway, S. J. Haswell, P. Styring, D. O. Morgan, B. Warrington and S. Y. F. Wong, *Analyst*, 2001, **126**, 11.
33 M. Sands, S. J. Haswell, S. M. Kelly, V. Skelton, D. O. Morgan, P. Styring and B. H. Warrington, *Lab Chip*, 2001, **1**, 64.

34 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Lab Chip*, 2001, **1**, 100.
35 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Lab Chip*, 2002, **2**, 62.
36 E. Garcia-Egido, S. Y. F. Wong and B. H. Warrington, *Lab Chip*, 2002, **2**, 170.
37 M. Fernandez-Suarez, S. Y. F. Wong and B. H. Warrington, *Lab Chip*, 2002, **2**, 31.
38 H. Lu, M. A. Schmidt and K. F. Jenson, *Lab Chip*, 2001, **1**, 22.
39 J. N. Pitts, R. L. Letsinger, R. P. Taylor, J. M. Patterson, G. Recktenwald and R. B. Martin, *J. Am. Chem. Soc.*, 1959, **81**, 1068.
40 R. C. R. Wootton, R. Fortt and A. J. de Mello, *Org. Proc. Res. Dev.*, 2002, **6**, 187.
41 P. Watts, C. Wiles, S. J. Haswell, E. Pombo-Villar and P. Styring, *Chem. Commun.*, 2001, 990.
42 P. Watts, C. Wiles, S. J. Haswell and E. Pombo-Villar, *Tetrahedron*, 2002, **58**, 5427.
43 L. A. Carpino and G. Y. Han, *J. Org. Chem.*, 1972, **37**, 3404.
44 L. A. Carpino, B. J. Cohen, K. E. Stephens, S. Y. Sadat-Aalaee, J-H. Tien and D. E. Langridge, *J. Org. Chem.*, 1986, **51**, 3732.
45 W. C. Chan, B. W. Bycroft, D. J. Evans and P. D. White, *J. Chem. Soc., Chem. Commun.*, 1995, 2209.
46 P. Watts, C. Wiles, S. J. Haswell and E. Pombo-Villar, *Lab Chip*, 2002, **2**, 141.
47 G. M. Greenway, S. J. Haswell, D. O. Morgan, V. Skelton and P. Styring, *Sens. Actuators B*, 2000, **63**, 153.
48 N. G. Wilson and T. McCreedy, *Chem. Commun.*, 2000, 733.
49 T. McCreedy and N. G. Wilson, *Analyst*, 2001, **126**, 21.
50 E. Dietzsch, D. Hönicke, M. Fichtner, K. Schubert and G. Weißmeier, *IMRET 4: 4th International Conference of Micro Reaction Technology Topical Conference Proceedings, AIChE Spring National Meeting*, March 5–9, 2000, Atlanta, GA, USA, p. 89.
51 S. Rozen, *Acc. Chem. Res.*, 1996, **21**, 307.
52 S. T. Purrington, B. S. Kagen and T. B. Patrick, *Chem. Rev.*, 1986, **86**, 997.
53 R. D. Chambers and R. C. H. Spink, *Chem. Commun.*, 1999, 883.
54 R. D. Chambers, D. Holling, R. C. H. Spink and G. Sandford, *Lab Chip*, 2001, **1**, 132.
55 R. D. Chambers, M. P. Greenhall and J. Hutchinson, *Tetrahedron*, 1996, **52**, 1.
56 R. D. Chambers, B. Grievson, F. G. Drakesmith and R. L. Powell, *J. Fluorine Chem.*, 1985, **29**, 323.
57 N. de Mas, R. J. Jackman, M. A. Schmidt and K. F. Jenson, *IMRET 5: Proceedings of the Fifth International Conference on Microreaction Technology*, Springer, Berlin, 2002, p. 60.
58 R. Srinivasan, I-M. Hsing, P. E. Berger, K. F. Jensen, S. L. Firebaugh, M. A. Schmidt, M. P. Harold, J. J. Lerou and J. F. Ryley, *AIChE J.*, 1997, **43**(11), 3059.
59 V. Hessel, , W. Ehrfeld, K. Golbig, C. Hofman, S. Jungwirth, H. Lowe, T. Richter, M. Storz and A. Wolf, *IMRET3: Proceedings of the third conference on microtechnology*, 2000, , 151.